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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/026,578	12/17/2001	Thomas Schmidt	10013.0014US	1170

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EXAMINER	
ROBINSON, HOPE A	

ART UNIT	PAPER NUMBER
1652	

MAIL DATE	DELIVERY MODE
11/24/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/026,578	SCHMIDT, THOMAS	
	Examiner	Art Unit	
	HOPE A. ROBINSON	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34,36,37,41-45 and 47-51* is/are pending in the application.

4a) Of the above claim(s) *1-15 and 18-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-17, 32-34, 36-37, 40-45 and 47-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. Applicant's response to the Office Action mailed February 26, 2008 on August 26, 2008 is acknowledged.

Claim Disposition

2. Claims 1-34, 36-37, 41-45 and 47-51 are pending. Claims 16-17 and 32-34, 36-37, 41-45 and 47-51 are under examination.

Maintained-Claim Rejections - 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 16-17, 32-34, 36-37, 40-45 and 47-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is directed to a fusion protein comprising a streptavidin-binding peptide linked to any protein (see for example claim 16) and the claims do not set forth a structure to make a correlation between structure and function. Note that claim 16 for example recites that the streptavidin binding peptide can be found at the carboxy or amino terminal of "a protein", however there is no description provided of a particular protein to know what the fusion protein will look like. The only description provided in claim 16 regarding the peptide is that its location in an unknown protein and that it comprises a sequential arrangement of at least two modules. Since at least has no upper limit this could mean 5 modules or 50 modules. Additionally the claimed invention is directed to a streptavidin mutein, any full-length protein, any protein fragment or any protein mutant. It is noted that claim 32 recites a binding affinity of "at least Kd greater than or equal to 10mM, however, no structure is provided for said fusion protein. In addition claim 16 as amended recites the structure of at least one of the modules of the streptavidin protein, however, this does not rectify the issue raised as the claims are directed to a streptavidin binding peptide linked to any unknown protein and comprises a sequential arrangement of at least two modules. A skilled artisan cannot envision the detailed chemical structure of the fusion protein as claimed absent adequate written description. The claims do not set forth what protein mutant is intended, only that it resulted from a deletion or substitution mutation. Therefore, the specification lacks adequate written description for the large variable genus of proteins encompassed in the claims.

Further, *Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir.1991)*, states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession of the invention*. The invention

is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116). The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. *See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993).*

4. Claims 16-17, 32-34, 36-37, 40-45 and 47-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification is not enabled for the full scope of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The enablement requirement refers to the requirement that the specification describe how to make and how to use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: Quantity of Experimentation Necessary; Amount of direction or guidance presented; Presence or absence of working examples; Nature of the Invention; State of the prior art and Relative skill of those in the art; Predictability or unpredictability of the art and

Breadth of the claims (see *In re Wands, 858 F.2d at 737, 8 USPQ2d at1404 (Fed. Cir. 1988*). The factors most relevant to the instant invention are discussed below.

The amount of experimentation required to practice the claimed invention because the instant specification is not commensurate in scope with the claims. The claimed invention is directed to a fusion protein comprising a streptavidin-binding peptide linked to any protein (see for example claim 16). Additionally the claimed invention is directed to a streptavidin mutein, any full-length protein, any protein fragment or any protein mutant. It is noted that claim 32 recites a binding affinity of "at least Kd greater than or equal to 10mM, however, no structure is provided for said fusion protein to make a correlation between structure and function. Claim 16 for example, recites the structure of at least one of the modules of the streptavidin protein which represents a partial structure, thus does not rectify the issue raised as the claims are directed to a streptavidin binding peptide linked to any unknown protein and comprises a sequential arrangement of at least two modules. The claims do not set forth what protein mutant is intended, only that it resulted from a deletion or substitution mutation. Therefore, the specification lacks adequate guidance for the large variable genus of proteins encompassed in the claims, thus undue experimentation would be required to practice the claimed invention.

A skilled artisan cannot predict that any known or unknown protein would bind to streptavidin, especially since protein families have different characteristics. Further, predictability of which potential changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (for example, expectedly intolerant to modification), and detailed knowledge of the ways in which

the protein's structure relates to its function. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, for example, multiple substitutions. In this case, the necessary guidance has not been provided in the specification. Therefore, while it is known in the art that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited, as certain positions in the sequence are critical to the protein's structure/function relationship. It is also known in the art that a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many cases. For example, various sites or regions directly involved in binding activity and in providing the correct three-dimensional spatial orientation of binding and active sites can be affected (see Wells, Biochemistry, vol. 29, pages 8509-8517, 1990). The instant specification provides no guidance/direction as to which regions of the protein would be tolerant of modifications and which would not, and it provides no working examples of any variant sequence that is encompassed by the claims. It is in no way predictable that randomly selected mutations, such as deletions, substitutions, additions, etc., in the disclosed sequences would result in a protein having activity comparable to the one disclosed. As plural substitutions for example are introduced, their interactions with each other and their effects on the structure and function of the protein is unpredictable. The skilled artisan would recognize the high degree of unpredictability that all the fragments/variants encompassed in the claims would retain the recited function.

Note that the state of the prior art provides evidence for the high degree of unpredictability as stated above. The specification lacks adequate guidance/direction to enable a

skilled artisan to practice the claimed invention commensurate in scope with the claims. Furthermore, while recombinant and mutagenesis techniques are known in the art, it is not routine in the art to screen large numbers of mutated proteins where the expectation of obtaining similar activity is unpredictable based on the instant disclosure. The amino acid sequence of a protein determines its structural and functional properties, and predictability of what mutations can be tolerated in a protein's sequence and result in certain activity, which is very complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's function from mere sequence data are limited, therefore, the general knowledge and skill in the art is not sufficient, thus the specification needs to provide an enabling disclosure.

The working examples provided do not rectify the missing information in the instant specification., thus the nature and properties of this claim is difficult to ascertain from the examples provided as one of skill in the art would have to engage in undue experimentation to construct all the mutants, muteins or fragments encompassed in the claimed invention and examine the same for function.

The specification does not provide support for the broad scope of the claims.. The issue in this case is the breath of the claims in light of the predictability of the art as determined by the number of working examples, the skill level artisan and the guidance presented in the instant specification and the prior art of record. This make and test position is inconsistent with the decisions of *In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)* where it is stated that "…scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art…". Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the

experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See *In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988)*. Thus, for all these reasons, the specification is not considered to be enabling for one skilled in the art to make and use the claimed invention as the amount of experimentation required is undue.

Maintained-Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

5. Claims 16-17 and 41, are rejected under 35 U.S.C. 102(e) as being anticipated by Skerra et al. U.S. Patent No.5,506,121, April 9, 1996).

Skerra et al. teach a fusion protein comprising a peptide (Trp-X-His-Pro-Gln-Phe-Z), wherein X represents any amino acid residue, Y and Z represents Gly, or where Y represents Glu and Z represents Arg or Lys (instant claim 16). Skerra et al. recites the sequence corresponding to the module set forth in SEQ ID NO:7 (claim 41 of the instant application); (see claims 1-2 of the patent). Therefore the limitations of the claims are met by the reference.

6. Claims 16-17, 32 and 41, are rejected under 35 U.S.C. 102(e) as being anticipated by Szostak et al. U.S. Patent No.6,841,359, October 31, 2008).

Szostak et al. teach a fusion protein comprising a protein of interest covalently linked to a peptide which binds streptavidin (SEQ ID NO:25; having "-His-Pro-Gln-Phe-" moiety with a specific disassociation constant), see claim 10 for instance in the patent. Therefore the limitations of the claims are met by the reference.

Response to Arguments

7. The response filed has been received and entered. Note that the 112 first paragraphs remain and have been amended based on the addition of new claims 48-51. Essentially the same argument is presented for the written description rejection as for the enablement rejection, therefore, the two rejections are discussed together herein. Applicant states that the claimed invention is directed to more than one module in a sequential arrangement and argue that the

claimed invention does not require further description and is enabled based on being affinity tags (stating that the focus should not be on the fusion protein structure *per se*). Amended claim 16 is directed to "A fusion protein comprising a streptavidin-binding peptide linked to a protein sequence of interest, wherein the streptavidin-binding peptide comprises a sequential arrangement of two modules, wherein the streptavidin-binding peptide is located at the carboxy terminal end or at the amino terminal end of the protein sequence of interest, wherein each module binds at least one of a streptavidin and a streptavidin mutein, wherein the modules are different or identical and each of the modules comprises an amino acid sequence -His-Pro-Baa- in which Baa is selected from the group consisting of glutamine, asparagine and methionine, and wherein at least one of the modules comprises a sequence -His-Pro-Gln-Phe- (SEQ ID NO:6)".

Note that the claim is to a fusion protein thus applicant' statement that the examiner should not focus on "the fusion protein structure per se" is not persuasive. In addition, applicant is arguing a limitation not present in the claim in statements made about the invention claiming an "affinity tag" as the claim does not recite such and is given the broadest reasonable interpretation. A structure-function correlation is essential and the partial structure provided in the claim is noted, however, the claim indicates that there is two modules which can be the same or different which is then fused to a protein of interest (unknown) and that it binds a streptavidin mutein (unknown). The invention is a fusion protein comprising a streptavidin-binding peptide and the claim broadly recites "streptavidin mutein" for example. In addition, the claim broadly reads on any fusion partner for example any streptavidin mutein fused to any protein; thus the claims encompass a genus of proteins not adequately described. Applicant argues that the fusion partner or the protein to which the streptavidin peptide is fused is not important. Applicant's

argument is not persuasive since the claim is directed to "a fusion protein comprising a streptavidin-binding peptide linked to a protein". The protein partner is important since binding might not occur depending on the fragment or variant thereof (see for example the variability contemplated in claim 17). The claims encompass any streptavidin mutein and any protein and its fragments or variants; absent any correlation between function and structure. Thus the rejection remains.

With regard to the art rejections, applicant states that the '121 patent has one module and the claimed invention is directed to two sequential modules. This argument is not persuasive as the patent outlines that "peptides" are made and fused and that they are normally 3 to 12 amino acids in length (see detailed description of the invention of '121 patent) which would inherently produce a sequential arrangement of two modules since the claimed invention indicates that one module can be "His-Pro-Baa" and can be the same or different. Note that SEQ ID NO:7 of the instant case which is taught by the reference has more than 6 amino acids, thus represents two sequential modules based on the "His-Pro-Baa" formula. Thus the reference is relevant. Applicants state that the '359 patent doesn't teach the limitation of the sequential modules. The same reasoning applied to the '121 patent can also be applied here as the reference teaches the disclosed sequences thus inherently has two sequential modules. Therefore, the rejections of record remain.

Conclusion

8. No claims are presently allowable.

9. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-0957. The examiner can normally be reached on Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat T. Nashed, Ph.D., can be reached at (571) 272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Hope A. Robinson/

Primary Examiner, Art Unit 1652